IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellants:	Frank A. Skraly and Martha Sholl		
Serial No.:	09/909,574	Art Unit:	1652
Filed:	July 20, 2001	Examiner:	Yong D. Pak
For:	*PRODUCTION OF POLYHYDROXYALKANOATES FROM POLYOLS*		

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SUBSTITUTE APPEAL BRIEF

Sir:

This is an appeal from the final rejection of claims 1-4 and 6-10 in the Office Action mailed September 21, 2005, maintained in the above-identified patent application. A Notice of Appeal was filed on December 21, 2005. An Advisory Action maintaining the rejections was mailed February 17, 2006. The Commissioner is hereby authorized to charge $500.00, the fee for the filing of this Appeal Brief for a large entity, to Deposit Account No. 50-3129. It is believed that no additional fee is required with this submission. However, should an additional fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-3129.

In response to the Notice of Defective Appeal Brief, two telephone calls to the examiner, and a telephone discussion with Mr. Craig Fineberg in the Office of the Board of Patent Appeals and Interferences, the heading labeled "(7) Grouping of Claims" has been deleted and the

headings "(8) Argument" and "(9) Summary and Conclusion" have been renumbered as "(7)" and "(8)" respectively. The rest of the Appeal Brief is unchanged as the undersigned is advised the form is correct.

(1) REAL PARTY IN INTEREST

The real party in interest of this application is Metabolix, Inc., the assignee.

(2) RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences known to appellants, the undersigned, or appellants' assignee which directly affects, which would be directly affected by, or which would have a bearing on the Board's decision in this appeal.

(3) STATUS OF CLAIMS

Claims 1-4 and 6-10 are pending. Claims 5 and 11-23 have been cancelled. Claims 1-4 and 6-10 are on appeal. The text of each claim on appeal, as pending, is set forth in an Appendix to this Appeal Brief.

(4) STATUS OF AMENDMENTS

A response after final rejection was filed via facsimile transmission on December 21, 2005. The claims were not amended in the response after final rejection. In the Advisory Action mailed February 17, 2006, the Examiner indicated that the rejections in the Final Office Action mailed September 21, 2005 would be maintained. The claims were last amended in the Amendment and Response filed July 8, 2005. An appendix sets forth the claims on appeal.

(5) SUMMARY OF CLAIMED SUBJECT MATTER

Independent claims 1 and 10 define a method for producing and a system for making, respectively, polyhydroxyalkanoates comprising providing organisms selected from the group consisting of bacteria, plants, and yeast (see at least page 5, lines 18-21), which express enzymes selected from the group consisting of acyl-CoA transferase, acyl-CoA synthetase, β-ketothiolase, acetoacetyl-CoA reductase, and PHA synthase (see at least page 5, lines 1-5), wherein the organisms are genetically engineered to express polynucleotides that encode enzymes (see at least page 3, lines 15-18), which are active in bacteria or plants, selected from the group consisting of diol oxidoreductase and aldehyde dehydrogenase (see at least page 4, lines 2-3, page 5, line 18 to page 6, line 28 and Examples 4 and 6), wherein the enzymes expressed by the organisms can convert diols into hydroxyalkanoate monomers selected from the group consisting of 4-hydroxybutyrate, 2-hydroxybutyrate, 4-hydroxyvalerate, 5-hydroxyvalerate, 6-hydroxyhexanoate, 2-hydroxyethanoate, 2-hydroxypropionate, and 3-hydroxyhexanoate (see at least page 2, line 22 to page 3, line 6 and claims 11 and 21 as originally filed), and culturing the organisms under conditions wherein the hydroxyalkanoate monomers are polymerized by the activity of a PHA synthase enzyme to form polyhydroxyalkanoates having a weight-average molecular weight (Mw) of at least 300,000 Da (see at least claims 1 and 11 as originally filed, page 4, lines 14-16 and the Examples).

Dependent claims 2, 3, 4, 6 and 7 define the diol as 1,6-hexanediol, 1,5-pentanediol, 1,4-butanediol, 1,2-ethanediol and 1,2-propanediol, respectively and the hydroxyalkanoate monomer as 6-hydroxyhexanoate, 5-hydroxyvalerate, 4-hydroxybutyrate, 2-hydroxyethanoate and 2-

hydroxypropionate (see at least page 2, line25 to page 3, line 3). Dependent claim 8 defines the method of claim 1 wherein the organism expresses polynucleotides which encode aldehyde dehydrogenase and diol oxidoreductase (see at least page 4, lines 2-3). Dependent claim 9 defines the method of claim 8 wherein the organism is selected from the group consisting of *Escherichia coli*, *Ralstonia eutropha*, *Klebsiella* spp., *Alcaligenes latus*, *Azotobacter* spp., and *Comamonas* spp. (see at least claim 9 as originally filed, page 1, lines 16-21, page 3, lines 18-22, page 5, lines 6-7 and page 6, lines 13-17).

(6) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The issues presented on appeal are:

(1) whether claims 1-4 and 6-10 are enabled as required by 35 U.S.C. § 112, first paragraph.

(2) whether claims 1-4 and 6-10 meet the written description requirement as required by 35 U.S.C. § 112, first paragraph.

(7) ARGUMENT

(i) The Claimed Methods and System

The claims of the present application define methods and system for producing polyhydroxyalkanoates comprising providing organisms with polynucleotides that encode enzymes, which are active in bacteria or plants, selected from diol oxidoreductase and aldehyde dehydrogenase, wherein the enzymes expressed by the organisms can convert diols into hydroxyalkanoate monomers.

The specification and the prior art disclose organisms that can be genetically engineered to produce PHAs (see at least page 5, lines 18-21), diols that may be utilized to form the claimed hydroxyalkanoate monomers (see at least page 9, lines 15-25), and organisms from which diol oxidoreductase and aldehyde dehydrogenase genes have been isolated and how to obtain these genes and enzymes (see at least page 6, lines 2-28 and Example 1). Methods for cloning genes encoding the enzyme are well known in the art and described in the application. For instance, Example 1 discusses a standard method for cloning the *aldH* gene from the *E. coli* genome using PCR. Similar methods can be used to clone aldehyde dehydrogenase and diol oxidoreductase genes from other organisms without undue experimentation. There is also sufficient direction and guidance given by the specification to construct plasmids and express the claimed genes (see Examples). In addition, the Appellants have provided working examples which demonstrate that one can use the claimed enzymes to engineer organisms to produce polyhydroxyalkanoates from diols, such as 1,4-butanediol (see Examples 3, 4 and 7) and 1,3-propanediol (see Examples 5 and 6).

(ii) Rejections under 35 U.S.C. § 112, first paragraph

(a) Written Description

The Examiner alleges claims 1-4 and 6-10 contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention for supposedly encompassing hydroxyalkanoates produced using any diol oxidoreductase, any aldehyde dehydrogenase, any plant and any diol.

The Legal Standard

The general standard for the written description requirement is that "a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention." *See* M.P.E.P. § 2163(I). The law has long allowed an appellant to claim all that he is entitled to, not forcing him to limit his claims to a specific example, if other means for achieving the same step would be known to those skilled in the art and not require undue experimentation.

"There is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed." *Wertheim*, 541 F.2d at 262, 191 USPQ at 96 (CCPA 1976). All that is required is that the specification provides sufficient description to reasonably convey to those skilled in the art that, as of the filing date sought, the inventor was in possession of the claimed invention. *Union Oil of California v. Atlantic Richfield Co.* , 208 F.3d 989, 997, 54 U.S.P.Q.2d 1227, 1232 (Fed. Cir. 2000); *Vas Cath*, 935 F.2d at 1563-64. An appellant may show possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). The written description requirement does not require a description of the complete structure of every species within a chemical genus. (*see Utter v. Hiraga*, 845 F.2d 993, 998, 6 U.S.P.Q.2d 1709, 1714 (Fed. Cir. 1988), stating "A specification may, within the meaning of 35 U.S.C. § 112, para. 1, contain a written description of a broadly claimed invention without describing all species that claim encompasses.").

An adequate written description of the invention may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention. *Id.*, citing *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323, 56 USPQ2d 1481, 1483 (Fed. Cir. 2000); *Pfaff v. Wells Electronics, Inc.*, 55 U.S. at 66, 119 S.Ct. at 311, 48 USPQ2d at 1646 (1998).

The written description is determined from the perspective of what the specification conveys to one skilled in the art citing *In re GPAC Inc.*, 57 F.3d 1573, 1579, 35 USPQ2d 1116, 1121 (Fed. Cir. 1995) and *Vas Cath*, 935 F.2d at 1563-64. Thus the specification need not always spell out every detail; only enough "to convince a person of skill in the art that the inventor possessed the invention and to enable such a person to make and use the invention without undue experimentation." *LizardTech Inc. v. Earth Resource Mapping, Inc.*, 424 F.3d 1336, 1344-34, 76 USPQ2d 1724, 1732 (Fed. Cir. 2005). In the patent context, not all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if, in the knowledge of the art, the disclosed function is sufficiently correlated to a particular, known structure. *Amgen v. Hoechst Marion Roussell* 314 F.3d 1313 (Fed.Cir. 2003).

Analysis

The written description requirement requires proof only that one of ordinary skill in the art could, or did, make and use the invention as described in the application. This is uncontroverted; the specification provides not only representative materials from a broad

spectrum of enzymes and substrates, but actual working examples. Therefore, appellants have complied with the written description requirement for the claimed methods and system.

The examiner seems to confuse the requirement for claiming organisms such as plants and enzymes *per se*, rather than a method of use that utilizes such organisms and enzymes having a defined specificity. This is legally incorrect.

Claims 1 and 10

Claims 1 and 10 define a method for producing and a system for making, respectively, polyhydroxyalkanoates comprising providing organisms selected from the group consisting of bacteria, plants, and yeast, which express enzymes selected from the group consisting of acyl-CoA transferase, acyl-CoA synthetase, β-ketothiolase, acetoacetyl-CoA reductase, and PHA synthase, wherein the organisms are genetically engineered to express polynucleotides that encode enzymes, which are active in bacteria or plants, selected from the group consisting of diol oxidoreductase and aldehyde dehydrogenase, wherein the enzymes expressed by the organisms can convert diols into hydroxyalkanoate monomers selected from the group consisting of 4-hydroxybutyrate, 2-hydroxybutyrate, 4-hydroxyvalerate, 5-hydroxyvalerate, 6-hydroxyhexanoate, 2-hydroxyethanoate, 2-hydroxypropionate, and 3-hydroxyhexanoate, and culturing the organisms under conditions wherein the hydroxyalkanoate monomers are polymerized by the activity of a PHA synthase enzyme to form polyhydroxyalkanoates having a weight-average molecular weight (Mw) of at least 300,000 Da.

As will be discussed in more detail below, it is clear that the claims are not drawn to genera of enzymes having any structure as alleged by the Examiner. The claimed genes and

enzymes were well known to those skilled in the art, commercially available and sufficiently identified in the specification as of the date of filing to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention.

The enzymes utilized in the method and system defined by the claims are well-known and exist within well-defined classes of proteins. The words "PHA synthase," "aldehyde dehydrogenase," "diol oxidoreductase," "acyl-CoA synthetase," "β-ketothiolase," "acetoacetyl-CoA reductase" and "acyl-CoA transferase," for example, classify proteins and readily convey distinguishing information concerning identity, *via* structure and function, such that one of ordinary skill in the art could easily visualize the identity of the members of each classification. In contrast to the term, for example, "cDNA" in which one of ordinary skill in the art would have great difficulty in ascertaining an actual sequence, each of the above-identified classes of protein readily convey an appropriate level of structure and function, especially in view of the sequences already disclosed in the specification and known in the art at the time of filing the present application.

One of ordinary skill in the art will absolutely agree that functional definitions **do** provide structural information commonly possessed by all members of each class. Over 30 years ago, Nobel Laureate Christian B. Anfinsen proved that a protein's "knowledge" of how to fold is stored in its sequence of amino acids. It is this folding that determines the protein's functionality (i.e. substrates recognized, reactions catalyzed, targeted protein binding, etc.). Conversely, a particular function can be directly attributed to particular folds determined by specific, or conserved, sequences of amino acids. It is well established in the art that structure–function

relationships do exist, and it is no more prevalent than within families of proteins, such as those that drive the specific reactions of claim 1. The written description requirement can be met by a functional description of claimed materials, if coupled with a known or disclosed correlation between function and structure. Appellants re-emphasize that a claim is not unpatentable simply because the "embodiments of the specification do not contain examples explicitly covering the full scope of the claim language." *LizardTech Inc., v. Earth Resource Mapping, Inc.* 424 F.3d at 1343; see also *Union Oil Co. v. Atlantic Richfield Co.*, 208 F.3d 989, 997, 54 USPQ2d 1227, 1232 (Fed. Cir. 2000).

Medline indicates that for each of these classes of enzymes, **the amino acid sequence and** a cDNA encoding the enzyme are known from multiple sources, but that the degree of homology is such that the known and available genes can be used to isolate additional genes from other sources encoding the enzymes. It is the amino acid sequence and protein function that allows for proper classification (i.e. synthase, dehydrogenase, oxidoreductase, etc.). ***If others*** (i.e. other proteins) are desirable, one of ordinary skill in the art may isolate the necessary genes using any of a number of techniques, including the use of oligonucleotide primers *designed to be complementary to the known sequence* (and/or degenerate primers) in conjunction with, for example, polymerase chain reaction (PCR). One of ordinary skill in the art will easily recognize that any asserted gaps between the present disclosure and claim breadth can be easily bridged; and will understand that any/all PHA biosynthetic enzymes that fall within each of the identified classes of enzymes (based upon already known amino acid sequence and function) could be used efficiently as reagents for production of glycolic acid-containing PHA polymers.

The Examiner is clearly overlooking that the written description is determined from the perspective of what the specification conveys to one skilled in the art citing *In re GPAC Inc.*, 57 F.3d 1573, 1579, 35 USPQ2d 1116, 1121 (Fed. Cir. 1995) and *Vas Cath*, 935 F.2d at 1563-64. The Examiner alleges that the genus comprising aldehyde dehydrogenase and the genus comprising diol oxidoreductase comprises species that are structurally unrelated and utilize substrates unrelated to the diols recited in the claims. The claims recite that the enzymes expressed by the organisms can convert diols into hydroxyalkanaote monomers. Therefore, the claims are limited to those enzymes that can perform the recited function and do not include enzymes that cannot use diols as substrates. Furthermore, the Examiner alleges that the claims are drawn to a genus of any diols. This is not correct. The claims are directed to a method or system where an organism can convert diols into 4-hydroxybutyrate, 2-hydroxybutyrate, 4-hydroxyvalerate, 5-hydroxyvalerate, 6-hydroxyhexanoate, 2-hydroxyethanoate, 2-hydroxypropionate, or 3-hydroxyhexanoate monomers. Therefore, the claims are not directed to *any* diols; the claims are directed to diols which lead to the production of **specific** hydroxyalkanoate monomers.

One of skill in the art would recognize that the appellants were in possession of the necessary common attributes or features of the elements possessed by the members of the genus of diols, plants, aldehyde dehydrogenase and diol oxidoreductase in view of the species disclosed.

The specification discloses at least at page 1, lines 21-23, page 2, line 25 to page 3, line 3 and page 4, numerous species of diols that can be used to produce the specific hydroxyalkanoate monomers defined by the claims.

The publications cited in the specification at least at page 6, lines 3-28, Skraly et al. *Appl. Environ. Microbiol.* 64:98-105 (1998); Daniel et al. *J. Bacteriol.* 177(8) 2151-2156 (1995); Leurs et al. *FEMS Microbiol. Lett.* 154(2): 337-345 (1997); Tong et al. *Appl. Environ. Microbiol.* 57(12):3541-3546 (1991); Yoshida et al. *Eur. J. Biochem.* 251:549-557 (1998) and op den Camp et al. *Plant Mol. Biol.* 35(3): 355-365 (1997) (submitted to the Examiner with the Information Disclosure Statement (IDS) filed April 29, 2002 and July 25, 2002 and with the Amendment and Response filed February 2, 2005 and enclosed herewith) demonstrate that the genes and enzymes can be obtained from a number of organisms and that sequence information for both aldehyde dehydrogenase and diol oxidoreductase were well known in the art as of the priority date of this application, July 21, 2000. The publications also demonstrate that the enzymes are active in bacteria and plants as required by the claims. Furthermore, actual DNA can be obtained from the authors of the publications or purchased from commercial suppliers, such as the American Type Culture Collection (ATCC). Published amino acid and nucleotide sequence listings for the various genes can also be obtained from GenBank or the National Center for Biotechnology Information (NCBI).

In addition to those nucleic acid sequences defined as specific *aldH* and *dhaT* genes in the specification, the primer and/or oligonucleotide sequences used to hybridize to, and isolate, those sequences can be used to isolate genes encoding aldehyde dehydrogenase and diol

oxidoreductase from other organisms. For example, the specification states that the *aldH* gene was cloned by PCR from the *E. coli* genome **on the basis of its homology with other aldehyde dehydrogenases** using the oligonucleotide primers SEQ ID NO: 3 and SEQ ID NO: 4 (Example 1 and specifically, page 9, lines 29-30). The same oligonucleotide primers could be used to isolate genes encoding aldehyde dehydrogenase from other bacterial strains. The same process can also be used to isolate diol oxidoreductases from a number of organisms. The specification at least at page 6, lines 3-28, discloses that there are a variety of organisms from which the aldehyde dehydrogenase and diol oxidoreductase genes can be isolated. The methods in which one of ordinary skill in the art would use to isolate the claimed genes lie at the very heart of defining the structural nature of each gene. The structures of the claimed genes are clearly limited based, in part, on the requirement for them to be complementary to the primers and/or oligos disclosed, for example, in Example 1.

It was also well known that a number of different organisms have the cellular machinery to produce polyhydroxyalkanoates, either endogenously, or through genetic engineering. For example, Madison and Huisman *Microbiol. Mol. Biol. Rev.* 63(1): 21-53 (1999) ("Madison"), which is recited in the specification on page 4, lines 1-2 (submitted to the Examiner with the IDS filed April 29, 2002 and enclosed herewith in the appendix), discusses the production of polyhydroxyalkanoates in bacteria (pages 37-40 and 41-44) and other microorganisms (pages 40-41), yeast (page 44), plants (page 45), insect cells (page 45), and animal tissues (page 45). Therefore, it is clear that the appellants were in possession of a wide range of species, including plant species, that could be used in the claimed methods and system.

It is clear from the discussion above that one of skill in the art would recognize that the appellants were in possession of the necessary common attributes or features of the elements possessed by the members of the genus of diols, plants, aldehyde dehydrogenase and diol oxidoreductase in view of the species disclosed. Therefore, claims 1 and 10 meet the written description requirement.

Claims 2, 3, 6 and 7

Dependent claims 2, 3, 6 and 7 define the specific diols as 1,6-hexanediol, 1,5-pentanediol, 1,2-ethanediol and 1,2-propanediol, respectively. Therefore, Appellants must only show possession for the genus of plants, aldehyde dehydrogenases and diol oxidoreductases. This Appellants have clearly done. Madison, which is recited in the specification on page 4, lines 1-2, discusses the production of polyhydroxyalkanoates in plants (page 45). Therefore, it is clear that the appellants were in possession of a wide range of plant species that could be used in the claimed methods and system. The specification and publications described above demonstrate that genes encoding aldehyde dehydrogenase and diol oxidoreductase were known and could be obtained from a number of organisms. Therefore, claims 2, 3, 6 and 7 meet the written description requirement.

Claim 4

Claim 4 states that the diol is 1,4-butanediol and the hydroxyalkanoate monomer is 4-hydroxybutyrate. The specification discloses at least at page 4, lines 3-5, that in the case of 1,4-butanediol, the diol oxidoreductase converts the substrate to 4-hydroxybutyraldehyde, which is then converted to 4-hydroxybutyrate by the aldehyde dehydrogenase. As described above, the

written description may be met by showing possession, which can be demonstrated by describing an actual reduction to practice of the claimed invention. The specification provides **actual working examples,** which show that the Appellants actually reduced the claimed method and system to practice. Specifically, at least at Example 3, the specification discloses production of poly(4-hydroxybutyrate) from 1,4-butanediol in bacteria, which have been genetically engineered to express an aldehyde dehydrogenase and a diol oxidoreductase. As discussed above, appellants were also in possession of a number of species of plants, aldehyde dehydrogenases and diol oxidoreductases. Therefore, Appellants have demonstrated that they were in possession of the methods and system defined by claim 4.

Claim 8

Claim 8 states that the organism expresses polynucleotides which encode aldehyde dehydrogenase and diol oxidoreductase. The main crux of the Examiner's arguments appears to be that the claims encompass diol oxidoreductases and aldehyde dehydrogenases that **may** not work. However, the Examiner has provided no evidence that the methods and system of the claims do not work nor does this unsupported argument have anything to do with complying with the written description requirement. In contrast, the Appellants have provided ample support demonstrating that the claims of the present application meet the written description requirement.

As discussed above, the specification and publications demonstrate that genes encoding aldehyde dehydrogenase and diol oxidoreductase were known and could be obtained from a number of organisms, as of the priority date of this application, July 21, 2000. In addition the

specification discloses that the *aldH* gene was cloned by PCR from the *E. coli* genome **on the basis of its homology with other aldehyde dehydrogenases** using the oligonucleotide primers SEQ ID NO: 3 and SEQ ID NO: 4 (Example 1 and specifically, page 9, lines 29-30). The same oligonucleotide primers could be used to isolate genes encoding aldehyde dehydrogenase from other bacterial strains. The same process can also be used to isolate diol oxidoreductases from a number of organisms. The specification at least at page 6, lines 3-28, discloses that there are a variety of organisms from which the aldehyde dehydrogenase and diol oxidoreductase genes can be isolated. The methods in which one of ordinary skill in the art would use to isolate the claimed genes lie at the very heart of defining the structural nature of each gene. Therefore, these enzymes are defined not only by their function, but also by their structure. Although not required by the written description standard, the specification also provides **actual working examples,** which show that the Appellants actually reduced the claimed method and system to practice. Specifically, at least at Example 3, the specification discloses production of poly(4-hydroxybutyrate) from 1,4-butanediol in bacteria. Therefore, Appellants have demonstrated that they were in possession of the methods and system defined by claim 8.

Claim 9

Claim 9 states that the organism is selected from *Escherichia coli*, *Ralstonia eutropha*, *Klebsiella* spp., *Alcaligenes latus*, *Azotobacter* spp., and *Comamonas* spp., which are all bacterial species. Since this claim is dependent upon claim 8, each of these bacteria must express an aldehyde dehydrogenase and a diol oxidoreductase. As discussed above, Example 3 demonstrates that Appellants actually reduced the claimed method and system to practice.

Specifically, Example 3 describes production of poly(4-hydroxybutyrate) from 1,4-butanediol in bacteria, which have been genetically engineered to express an aldehyde dehydrogenase and a diol oxidoreductase. The Examiner has not rejected the claims for lack of written description for the genus of bacteria. Therefore, claim 9 must only show possession for the genus of aldehyde dehydrogenases, diols and diol oxidoreductases. Since the claims are directed to diols which lead to the production of **specific** hydroxyalkanoate monomers, the claims satisfy the written description requirement. Furthermore, the specification and publications discussed above demonstrate that genes encoding aldehyde dehydrogenase and diol oxidoreductase were known and could be obtained from a number of organisms. Therefore, Appellants have demonstrated that they were in possession of the methods and system defined by claim 9.

Summary of Arguments regarding Written Description

As discussed above, the claims comply with the written description requirement. In a recent decision by this Board relating to another application in this general field, U.S.S.N. 09/364,847, the examiner had made a similar rejection and the Board found that the claims complied with the written description requirement, based on the following analysis:

We appreciate the examiner's concerns with respect to the claims being directed to a genus of enzymes which are described by their function; however, we find that, in the case before us, the specification reasonably conveys to one skilled in the art that the appellants were in possession of the invention at the time the application was filed. Union Oil of California v. Atlantic Richfield Co., 208 F.3d at 997; Vas-Cath Inc. v. Mahurkar, 935 F.2d at 1563-64; In re Gosteli, 872 F.2d at 1012; In re Edwards, 568 F.2d at 1351-52. Here, it appears that the examiner has studied the appellants' disclosure and formulated a conclusion as to what he (the examiner) regards as the broadest possible invention, and then determined that the appellants' claims are directed to an invention which is broader than that which is described in the specification. This analysis is improper. We remind the examiner that written description is determined from the perspective of what the specification conveys to one skilled in the art. In re GPAC Inc., 57 F.3d 1573, 1579, 35 USPQ2d 1116, 1121 (Fed. Cir. 1995); Vas-Cath Inc. v. Mahurkar, 935 F.2d at 1563-64. Thus, the specification need not always spell out every detail; only enough "to convince a person of skill in the art that the inventor possessed the invention and to enable such a person to make and use the invention without undue experimentation." LizardTech Inc., v. Earth Resource Mapping, Inc., 424 F.3d 1336, 1344-45, 76 USPQ2d 1724, 1732 (Fed. Cir. 2005).

However, a claim is not unpatentable simply because the "embodiments of the specification do not contain examples explicitly covering the full scope of the claim language." LizardTech Inc., v. Earth Resource Mapping, Inc., 424 F.3d at 1343; see also, Union Oil Co. v. Atlantic Richfield Co., 208 F.3d 989, 997, 54 USPQ2d 1227, 1232 (Fed. Cir. 2000). As discussed above, a patent application is written for a person of skill in the art. In re GPAC Inc., 57 F.3d at 1579; Vas-Cath Inc. v. Mahurkar, 935 F.2d at 1563-64. Since the evidence of record demonstrates that the claimed classes of enzymes were well known in the art (pages 8-10 of the specification; pages 4-8 of the appellants' response (Jan. 2, 2003)), we find that one skilled in the art would readily recognize the enzymes involved in the PHA biosynthetic pathway even if they are derived from different microorganisms and there are minor differences in the amino acid sequences. Accordingly, we find that the appellants were in possession of the claimed invention at the time the application was filed. Vas-Cath Inc. v. Mahurkar, 935 F.2d at 1563-64.

This same analysis is equally applicable here. Since the enzymes were known, their substrate specificity known, the nucleotide sequences encoding the enzymes known and production of PHAs in genetically engineered bacteria and plants well established, and appellants established through representative working examples that they had possession of the claimed invention, the claims must comply with the written description requirement.

(b) Enablement

The Examiner alleges claims 1-4 and 6-10 are not enabled for methods of producing polyhydroxyalkanoates from hydroxyalkanoates using any diol oxidoreductases and any aldehyde dehydrogenases by converting any diols to hydroxyalkanoates in any plants.

The Legal Standard

The Court of Appeals for the Federal Circuit (CAFC) has described the legal standard for enablement under § 112, first paragraph, as whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation. See, e.g., *Amgen v. Hoechst Marion Roussell* 314 F.3d 1313 (Fed. Cir. 2003) and *Genentech, Inc. v. Novo Nordisk A/S*, 108 F3d at 165, 42 USPQ2d at 1004 (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). See also *In re Fisher*, 427 F.2d at 839, 166 USPQ at 24; *United States v. Telectronics, Inc.*, 857 F.2d 778 (Fed. Cir. 1988); and *In re Stephens*, 529 F.2d 1343 (CCPA 1976). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *M.I.T. v. A.B. Fortia* , 774 F.2d 1104 (Fed. Cir. 1985). The adequacy of a specification's description is not necessarily defeated by the need for some experimentation to determine the properties of a claimed product. *See Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F3d 956, 965-966 63 USPQ2d 1609, 1614 (Fed. Cir. 2002). In addition, a patent need not teach, and preferably omits, what is well known in the art. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *citing Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 U.S.P.Q.

481, 489 (Fed. Cir. 1984). Thus, information that is conventional or well-known to one of ordinary skill in the art need not be disclosed by the specification.

Whether the disclosure is enabling is a legal conclusion based upon several underlying factual inquiries. See *In re Wands*, 858 F.2d 731, 735, 736-737, 8 USPQ2d 1400, 1402, 1404 (Fed. Cir.1988). As set forth in *Wands*, the factors to be considered in determining whether a claimed invention is enabled throughout its scope without undue experimentation include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims. In cases that involve unpredictable factors, "the scope of the enablement obviously varies inversely with the degree of unpredictability of the factors involved." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation "must not be unduly extensive." *In re Atlas Powder Co., v. E.I. DuPont De Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir.1984).

As noted in *Ex parte Jackson*, the test is not merely quantitative, since a considerable amount of experiment is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed. *Ex parte Jackson*, 217 USPQ 804, 807 (PTO Bd. App. 1982). There is no requirement for examples. *In re Borkowski*, 422 F.2d 904, 57 C.C.P.A. 946

(C.C.P.A. 1970). Further, patent appellants are not required to disclose every species encompassed by their claims, even in an unpredictable art. *In re Vaeck,* 947 F.2d 488, (Fed. Cir. 1991). As set forth in *Johns Hopkins Univ. v. CellPro Inc.,* 152 F.3d 1342, 1361, 47 USPQ2d 1705, 1714 (Fed. Cir. 1998), "the enablement requirement is met if the description enables **any** mode of making and using the invention."

Analysis

A proper analysis of the *Wands* factors shows that the claims satisfy the enablement requirement. The courts have indicated that some experimentation is permitted as long as such experimentation is not undue. As stated in *MIT v. A.B. Fortia,* " The fact that experimentation may be complex does not make it undue if the art typically engages in such experimentation".

It clear from the amount of direction or guidance presented in the specification, the presence of working examples, the state of the prior art, and the relative skill in the art that one of ordinary skill in the art would be able to make and use the claimed genetically engineered organisms for the production of polyhydroxyalkanoates **without** undue experimentation.

Claims 1 and 10

Claims 1 and 10 define a method for producing and a system for making, respectively, polyhydroxyalkanoates comprising providing organisms selected from the group consisting of bacteria, plants, and yeast, which express enzymes selected from the group consisting of acyl-CoA transferase, acyl-CoA synthetase, β-ketothiolase, acetoacetyl-CoA reductase, and PHA synthase, wherein the organisms are genetically engineered to express polynucleotides that encode enzymes, which are active in bacteria or plants, selected from the group consisting of diol

oxidoreductase and aldehyde dehydrogenase, wherein the enzymes expressed by the organisms can convert diols into hydroxyalkanoate monomers selected from the group consisting of 4-hydroxybutyrate, 2-hydroxybutyrate, 4-hydroxyvalerate, 5-hydroxyvalerate, 6-hydroxyhexanoate, 2-hydroxyethanoate, 2-hydroxypropionate, and 3-hydroxyhexanoate, and culturing the organisms under conditions wherein the hydroxyalkanoate monomers are polymerized by the activity of a PHA synthase enzyme to form polyhydroxyalkanoates having a weight-average molecular weight (Mw) of at least 300,000 Da.

As discussed above, the Examiner alleges that the claims encompass any diol oxidoreductases, any aldehyde dehydrogenase and any diols. This is clearly incorrect. The claims are clearly limited to those enzymes that can convert diols into hydroxyalkanoate monomers and do not include enzymes that cannot use diols as substrates. One of ordinary skill in the art would **not** select an enzyme that cannot use diols as substrates in the methods defined by the claims. Furthermore, the claims are directed to diols which lead to the production of the **specific** hydroxyalkanoate monomers 4-hydroxybutyrate, 2-hydroxybutyrate, 4-hydroxyvalerate, 5-hydroxyvalerate, 6-hydroxyhexanoate, 2-hydroxyethanoate, 2-hydroxypropionate, or 3-hydroxyhexanoate.

The specification and the prior art disclose organisms that can be genetically engineered to produce PHAs (page 5, lines 18-21). Specifically, the specification discloses that the same genes that are described in the specification and the examples may be introduced into eukaryotic cells such as plant cells. The specification discloses at least at page 5, lines 23-26 that genes and techniques for developing recombinant PHA producers, such as plants, are generally known to

those of skill in the art, and cite Madison and WO 99/14313 to Metabolix, Inc. For example, Madison, a copy of which is enclosed in the Appendix, discusses the production of polyhydroxyalkanoates in plants at least at page 45 and demonstrates that one of skill in the art was capable of making and using genetically engineered plants for production of PHAs at the time this application was filed. The specification also discloses at the bottom of page 5 that because all the genes necessary to implement the production of PHAs from feedstock such as diols have been cloned and are available in genetically manipulatable form, any combination of plasmid-borne and integrated genes may be used in the production of PHAs in organisms such as plants. Examples of such plasmids and methods for making them are described in the specification at least in the Examples.

Diols that may be utilized to form the claimed hydroxyhexanoate monomers are disclosed in the specification at least at page 9, lines 15-25. Furthermore, the specification provides guidance for using the diols at least at page 4, lines 26-29, "the diol can be fed to the cells wither during growth or after a separate growth phase, either alone or in combination with at least one other feedstock." The examples also provides guidance for using diols.

The specification also discloses organisms from which diol oxidoreductase and aldehyde dehydrogenase genes have been isolated and how to obtain these genes and enzymes (page 6, lines 2-28; Example 1). In addition, the assignee has two issued patents, U.S. Patent No. 6,329,183 and U.S. Patent No. 6,576,450, with claims directed to the production of PHAs by providing diols to genetically engineered organisms (although the patents do not disclose the claimed subject matter). These patents were brought to the attention of the Examiner in the

Amendment and Response filed February 2, 2005 copies of which are enclosed in the Appendix. Once a gene is identified, it is routine in the art to incorporate the gene into a plasmid for expression in cells. There is sufficient direction and guidance given by the specification to construct plasmids and express the claimed genes (see Examples). In addition, the experimental protocols are routine in the art and expression vectors, restriction enzymes and ligation enzymes are also commercially available.

Although there is no requirement for examples, Appellants have provided numerous working examples which not only demonstrate that one can use the claimed enzymes to engineer organisms to produce polyhydroxyalkanoates from diols, such as 1,4-butanediol (Examples 3, 4 and 7) and 1,3-propanediol (Examples 5 and 6), but that one can isolate the desired enzymes with only routine experimentation. For instance, Example 1 discusses a standard method for cloning the *aldH* gene from the *E. coli* genome using PCR, and Heim and Strehler, *Gene* 99(1):15-23 (1991) (the abstract of which was provided to the Examiner in the Amendment and Response filed February 2, 2005, a copy of which is enclosed in the Appendix) demonstrates the cloning of an *E. coli* gene encoding an ALDH, remarkably similar to mammalian aldehyde dehydrogenases, in 1991! Similar methods can be used to clone diol oxidoreductase genes and would have been routine to one of skill in the art as of the July 21, 2000 priority date of this application.

Furthermore, the enzymes may be selected based on their substrate specificity. As discussed at page 6, lines 24-28, of the specification, "The choice of an appropriate aldehyde dehydrogenase for use in metabolic engineering should be done after evaluation of the substrate specificity of several candidates. Enzyme assays such as that described in Baldom & Aguilar

(1987, J. Biol. Chem. 262:13991-6 (cited in the Amendment and Response filed February 2, 2005 and enclosed herewith in the Appendix)) are useful for such diagnoses." The substrate, in the presence of its cognate active enzyme, will be readily converted into product. Based upon the specification, the cited reference, and the Examples one of ordinary skill in the art will appreciate that assays for enzyme specificity and the presence, or production, of end-product (i.e. polyhydroxyalkanoate) is easily measured and characterized.

There is no legal requirement that all of the enzymes within the scope of the claims convert the diols to their corresponding hydroxyalkanoate monomers for the enzymes to have the specified utility. As noted above, the claims are enabled if the description enables any mode of making and using the invention. This the specification clearly does, which is acknowledged by the Examiner on page 10 of the Office Action. In *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.* (1984), the Federal Circuit noted that "Even if some of the claimed combinations were inoperative, the claims are not necessarily invalid ... [I]f the number of inoperative combinations becomes significant, and in effect forces one of ordinary skill in the art to experiment unduly in order to practice the claimed invention, the claims might indeed be invalid." *Atlas Powder Co. v. E. I. Du Pont de Nemours & Co.*, 750 F.2d 1569 (Fed. Cir.1984). However, this is clearly not the case in the present application. It would only take routine experimentation, such as the screening methods described on page 7, line 24 to page 8, line 26, to identify other aldehyde dehydrogenases and diol oxidoreductases, for example, from the organisms recited on page 6, lines 3-28, that can convert the diols to their corresponding hydroxyalkanoates. Based on teachings in the specification and the state of the art, one of ordinary skill in the art would be

able to select an appropriate aldehyde dehydrogenase or diol oxidoreductase for use in the claimed methods and system.

Even if the examiner has provided a rational basis for making a *prima facie* case that the claims are not enabled (which is believed not to be the case since all the examiner has provided is argumentation, not support for the rejection), it is clear from the discussion above that Appellants have provided sufficient evidence in to rebut the rejections. The Examiner has not provided Appellants with any evidence to contradict Appellants' evidence supporting enablement of the claims. *This is legal error.* Once the appellants' have rebutted the rejection with evidence, the examiner must provide a basis, not argumentation, for why the rejection has been maintained. *The examiner has failed to do so.*

It clear from the amount of direction or guidance presented in the specification, the presence of working examples, the state of the prior art, the relative skill in the art, and the breadth of the claims that one of ordinary skill in the art would be able to make and use the claimed genetically engineered organisms for the production of polyhydroxyalkanoates without undue experimentation. Therefore, claims 1 and 10 are enabled.

Claims 2, 3, 6 and 7

Dependent claims 2, 3, 6 and 7 define the specific diols as 1,6-hexanediol, 1,5-pentanediol, 1,2-ethanediol and 1,2-propanediol, respectively. Therefore, Appellants must only show enablement for the use of plants, aldehyde dehydrogenases and diol oxidoreductases. This Appellants have clearly done. Madison, which is recited in the specification on page 4, lines 1-2, discusses the production of polyhydroxyalkanoates in plants (page 45). Therefore, it is clear that

one of skill in the art could make and use plant species in the claimed methods and system for production of polyhydroxyalkanoates. As discussed above, based on teachings in the specification and the state of the art, one of ordinary skill in the art would be able to select an appropriate aldehyde dehydrogenase or diol oxidoreductase for use in the claimed methods and system. Therefore, claims 2, 3, 6 and 7are enabled.

Claim 4

Claim 4 states that the diol is 1,4-butanediol and the hydroxyalkanoate monomer is 4-hydroxybutyrate. Therefore, Appellants must only show enablement for the use of plants, aldehyde dehydrogenases and diol oxidoreductases. As discussed above, it is clear that one of skill in the art could make and use plant species in the claimed methods and system for production of polyhydroxyalkanoates. One of ordinary skill in the art would also be able to select an appropriate aldehyde dehydrogenase or diol oxidoreductase for use in the claimed methods and system. In addition, the specification provides specific guidance at least at page 4, lines 3-5, that in the case of 1,4-butanediol, the diol oxidoreductase converts the substrate to 4-hydroxybutyraldehyde, which is then converted to 4-hydroxybutyrate by the aldehyde dehydrogenase. At least at Example 3, the specification provides an actual working example of production of poly(4-hydroxybutyrate) from 1,4-butanediol in bacteria, which have been genetically engineered to express an aldehyde dehydrogenase and a diol oxidoreductase. Therefore, claim 4 is enabled.

Claim 8

Claim 8 states that the organism expresses polynucleotides which encode aldehyde dehydrogenase and diol oxidoreductase. As discussed above, the specification and publications demonstrate that genes encoding aldehyde dehydrogenase and diol oxidoreductase were known and could be obtained from a number of organisms, as of the priority date of this application, July 21, 2000. In addition the specification discloses that the *aldH* gene was cloned by PCR from the *E. coli* genome **on the basis of its homology with other aldehyde dehydrogenases** using the oligonucleotide primers SEQ ID NO: 3 and SEQ ID NO: 4 (Example 1 and specifically, page 9, lines 29-30). The same oligonucleotide primers could be used to isolate genes encoding aldehyde dehydrogenase from other bacterial strains. The same process can also be used to isolate diol oxidoreductases from a number of organisms. The specification at least at page 6, lines 3-28, discloses that there are a variety of organisms from which the aldehyde dehydrogenase and diol oxidoreductase genes can be isolated. In addition, at least at Example 3, the specification provides an actual working example of production of poly(4-hydroxybutyrate) from 1,4-butanediol in bacteria, which have been genetically engineered to express an aldehyde dehydrogenase and a diol oxidoreductase. Therefore, claim 8 is enabled.

Claim 9

Claim 9 states that the organism is selected from *Escherichia coli*, *Ralstonia eutropha*, *Klebsiella* spp., *Alcaligenes latus*, *Azotobacter* spp., and *Comamonas* spp., which are all bacterial species. The Examiner states at page 7 of the Office Action mailed September 21, 2005 that the claims are enabled for the genus of bacteria. Therefore, Appellants must only demonstrate

enablement for diols, aldehyde dehydrogenases and diol oxidoreductases. The Examiner also states that the claims are enabled for *aldH* from *E. coli* and *dhaT* from *K. pneumoniae*. As discussed above, one of skill in the art could readily identify other aldehyde dehydrogenases and diol oxidoreductases for use in the methods and system as defined by the claims. Finally, the claims are directed to diols which lead to the production of **specific** hydroxyalkanoate monomers and are not directed to any diols as alleged by the Examiner. As also discussed above, the enablement requirement is met if the description enables **any** mode of making and using the invention. Example 3 demonstrates that Appellants made and used the claimed method and system. Specifically, Example 3 describes production of poly(4-hydroxybutyrate) from 1,4-butanediol in bacteria, which have been genetically engineered to express an aldehyde dehydrogenase and a diol oxidoreductase. Therefore, claim 9 is enabled.

(8) SUMMARY AND CONCLUSION

1. The written description requirement requires proof only that one of ordinary skill in the art would believe the appellants had possession of the claimed invention at the time of filing of the application. This is uncontroverted. The specification provides not only representative materials from a broad spectrum of enzymes and substrates, but actual working examples. One of skill in the art would recognize that the appellants were in possession of the necessary common attributes or features of the elements possessed by the members of the genus of diols, plants, aldehyde dehydrogenase and diol oxidoreductase in view of the species disclosed. Therefore, appellants have complied with the written description requirement for the claimed methods and system.

2. The legal requirement is not to prove enablement for each and every species that may fall within the scope of the claim. Even if the examiner has provided a rational basis for making a *prima facie* case that the claims are not enabled (which is believed not to be the case since all the examiner has provided is argumentation, not support for the rejection), Appellants have provided sufficient evidence in to overcome all of the Examiner's concerns. It clear from the amount of direction or guidance presented in the specification, the presence of working examples, the state of the prior art, the relative skill in the art, and the breadth of the claims that one of ordinary skill in the art would be able to make and use the claimed genetically engineered organisms for the production of polyhydroxyalkanoates without undue experimentation. Therefore, claims 1-4 and 6-10 are enabled.

For the foregoing reasons, Appellants submit that claims 1-4 and 6-10 are patentable.

Respectfully submitted,

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Claims Appendix: Claims On Appeal

1. A method for producing polyhydroxyalkanoates comprising providing organisms selected from the group consisting of bacteria, plants, and yeast, which express enzymes selected from the group consisting of acyl-CoA transferase, acyl-CoA synthetase, β-ketothiolase, acetoacetyl-CoA reductase, and PHA synthase, wherein the organisms are genetically engineered to express polynucleotides that encode enzymes, which are active in bacteria or plants, selected from the group consisting of diol oxidoreductase and aldehyde dehydrogenase, wherein the enzymes expressed by the organisms can convert diols into hydroxyalkanoate monomers selected from the group consisting of 4-hydroxybutyrate, 2-hydroxybutyrate, 4-hydroxyvalerate, 5-hydroxyvalerate, 6-hydroxyhexanoate, 2-hydroxyethanoate, 2-hydroxypropionate, and 3-hydroxyhexanoate, and culturing the organisms under conditions wherein the hydroxyalkanoate monomers are polymerized by the activity of a PHA synthase enzyme to form polyhydroxyalkanoates having a weight-average molecular weight (Mw) of at least 300,000 Da.

2. The method of claim 1 wherein the diol is 1,6-hexanediol and the hydroxyalkanoate monomer is 6-hydroxyhexanoate.

3. The method of claim 1 wherein the diol is 1,5-pentanediol and the hydroxyalkanoate monomer is 5-hydroxyvalerate.

4. The method of claim 1 wherein the diol is 1,4-butanediol and the hydroxyalkanoate monomer is 4-hydroxybutyrate.

6. The method of claim 1 wherein the diol is 1,2-ethanediol and the hydroxyalkanoate monomer is 2-hydroxyethanoate.

7. The method of claim 1 wherein the diol is 1,2-propanediol and the hydroxyalkanoate monomer is 2-hydroxypropionate.

8. The method of claim 1 wherein the organism expresses polynucleotides which encode aldehyde dehydrogenase and diol oxidoreductase.

9. The method of claim 8 wherein the organism is selected from the group consisting of *Escherichia coli*, *Ralstonia eutropha*, *Klebsiella* spp., *Alcaligenes latus*, *Azotobacter* spp., and *Comamonas* spp.

10. A system for making polyhydroxyalkanoates comprising organisms selected from the group consisting of bacteria, plants, and yeast , which express enzymes selected from the group consisting of acyl-CoA transferase, acyl-CoA synthetase, β-ketothiolase, acetoacetyl-CoA reductase, and PHA synthase, wherein the organism is genetically engineered to express polynucleotides that encode enzymes, which are active in bacteria or plants, selected from the group consisting of diol oxidoreductase and aldehyde dehydrogenase, wherein the enzymes expressed by the organisms can convert diols into hydroxyalkanoate monomers selected from the group consisting of 4-hydroxybutyrate, 2-hydroxybutyrate, 4-hydroxyvalerate, 5-hydroxyvalerate, 6-hydroxyhexanoate, 2-hydroxyethanoate, 2-hydroxypropionate, and 3-hydroxyhexanoate, wherein the monomers are polymerized by the activity of a PHA synthase enzyme to form polyhydroxyalkanoates having a weight-average molecular weight (Mw) of at least 300,000 Da.

Evidence Appendix

1. Skraly et al., *Appl. Environ. Microbiol.* 64:98-105 (1998)
2. Daniel et al., *J. Bacteriol.* 177(8) 2151-2156 (1995)
3. Leurs et al., *FEMS Microbiol. Lett.* 154(2): 337-345 (1997)
4. Tong et al., *Appl. Environ. Microbiol.* 57(12):3541-3546 (1991)
5. Yoshida et al., *Eur. J. Biochem.* 251:549-557 (1998)
6. op den Camp et al., *Plant Mol. Biol.* 35(3): 355-365 (1997)
7. Madison and Huisman, *Microbiol. Mol. Biol. Rev.* 63(1): 21-53 (1999)
8. Heim and Strehler, *Gene* 99(1):15-23 (1991) (abstract)
9. Baldom and Aguilar, *J. Biol. Chem.* 262:13991-6 (1987)
10. U.S. Patent No. 6,329,183 to Metabolix, Inc.
11. U.S. Patent No. 6,576,450 to Metabolix, Inc.

Related Proceedings Appendix

NONE.

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